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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/491,896	DURING, MATTHEW J.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44,47-69 and 77-109* is/are pending in the application.

4a) Of the above claim(s) *1-44,47-69 and 77-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-44,47-69 and 77-109* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 11 February 2003 (Paper No. 20) has been entered in full. Claims 1, 6, 9, 22, 24-25, 29, 36, 38, 41, 54, 59, 68, 86, 91, 95, 98, 102, and 105 are amended. Claims 70-72 and 74-76 are cancelled. Claim 109 is added.

Election/Restrictions

In the previous Office Action (Paper No. 18, 01 October 2002), the Examiner indicated that Applicant's response of 02 July 2002 was not responsive because the amended claims were directed to an invention that was patentably distinct from the invention that was already examined. In the current response of 11 February 2003, Applicant asserts that this application was subject to a Restriction requirement pursuant to Paper No. 6 to which the invention of Group I was elected (claims directed to treatment of a neurological disorder by administering a vaccine). Applicant contends that the amendments to the claims do not depart from this election, but rather represent several genus level claims that encompass both the elected subject matter and other aspects of the invention. Applicant argues that the claims are not redirected to a patentably distinct invention. Applicant submits that genus level linking claims have been presented, which Applicant is legally entitled to do at any stage in prosecution.

Applicant's arguments have been fully considered but are not found to be persuasive. To begin with, the restriction requirement of Paper No. 6 (07 September 2000) indicated that Group I was drawn to "a method of treatment, improvement, or modification of a neurological disorder or protein comprising administering an *amino acid vaccine* comprising a therapeutically effective amount of antigen...". Group I was not directed to the administration of any general

vaccine, but rather the administration of an amino acid vaccine comprising an antigen. The amended claims now recite "inducing the presence of a therapeutically effective amount of an antigen" while other claims recite that the antigen is induced by different types of vaccines, including viral vector, DNA, and peptide. Essentially, most of the currently amended claims (such as claim 1) do depart from the originally elected claims because there is no recitation of how an antigen is induced in the circulatory system of the subject. For example, is DNA, specific peptides, inorganic compounds, agonists, antagonists, antibodies administered to a subject? The originally filed claims specifically recited "administering a vaccine comprising a therapeutically effective amount of antigen". Furthermore, the other claims (such as claim 9) that recite administering a type of vaccine, still depart from the originally elected claims because the antigen itself is not being administered. Although claim 9 mentions that a crude antigen vaccine is one of the vaccines that could be administered, there is no indication that this is the antigen that is induced. Another non-related antigen could possibly induce the presence of a therapeutically effective amount of the antigen in the claims.

Applicant is legally entitled to present genus level linking claims. However, the species that the genus level linking claims are attempting to encompass (any method of inducing an antigen in the circulatory system), were never speciated in the restriction of 07 September 2000 (Paper No. 6). The originally filed method claims were restricted into different *groups* based on the administration of an amino acid vaccine or nucleic acid vaccine that comprises an antigen. It also cannot be determined from the currently amended claims if the antigen that is induced in the circulatory system is endogenous to the subject or is administered. Additionally, had the currently amended claims been presented in the originally filed specification, the Examiner

would have put these claims into a separate group other than Group I because the new claims require search and consideration of induction of the presence of an antigen in the circulatory system in a subject, which is not required by the elected invention of Group I. Group I requires search and consideration of efficacy of administration of amino acid vaccine therapy. Therefore, claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, and 86-108 are directed to an invention that is independent or distinct from the invention originally claimed.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, and 86-108 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

This application contains claims 4, 13-21, 33-35, 47-53, 55-58, 62-67, and 77-85 drawn to an invention nonelected with traverse in Paper No. 8 (06 December 2000).

A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 109 is under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification as set forth at pg 3 of the previous Office Action (Paper No. 16, 27 February 2002) are *withdrawn* in view of the amended title (Paper No. 17, 02 July 2002).

2. The objections to claim 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, 70-72, 74-76, and 86-108 as set forth at pg 3 of the previous Office Action (Paper No. 16, 27 February 2002) are *withdrawn* in view of the withdrawn claims.

3. The rejection of claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, 70-72, 74-76, and 86-108 under 35 U.S.C. § 112, first paragraph (enablement) as set forth at pg 4-12 of the previous Office Action (Paper No. 16, 27 February 2002) are *withdrawn* in view of the cancelled and withdrawn claims. Please see section on 35 U.S.C. § 112, first paragraph, below.

4. The rejections to claims 70-72 and 74-76 under 35 U.S.C. 112, second paragraph, as set forth at pg 12 of the previous Office Action (Paper No. 16, 27 February 2002) are *withdrawn* in view of the cancelled claims (Paper No. 17, 02 July 2002).

5. The rejection to claims 70-72 and 74-76 under 35 USC § 102(b), as set forth at pg 12-13 is *withdrawn* in view of the cancelled claims (Paper No. 17,02 July 2002).

Claim Rejections - 35 USC § 112, first paragraph

6. Claims 109 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, claim 109 recites a method for modifying the function of a target receptor associated with a neurological disorder in a subject comprising administering a vaccine comprising a therapeutically effective amount of an N-methyl-D-aspartate receptor subunit 1 (NMDAR1) antigen into the circulatory system of the subject, wherein the antigen elicits the production of antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and bind to a target receptor located on a neuronal cell in

the central nervous system of the subject and associated with a neurological disorder, and modify the function of the target receptor.

Applicant's arguments (Paper No. 20,11 February 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts at pg 25 of the Response (11 February 2003) that the claims are sufficiently enabled by the specification to provide one of ordinary skill in the art with adequate guidance to modify the function of a target receptor associated with a neurological disorder, a neuroendocrine disorder, or cognition by raising antibodies against a CNS antigen present in the circulatory system of a subject. Applicant asserts that the specification of the instant application at pg 30-35 describes in detail how the presence of a central nervous system antigen can be induced in the circulatory system of a subject. Applicant also submits that the specification discloses methods on the indirect administration of the antigen, for example, by the delivery of DNA encoding the CNS antigen, which can then be used to express the antigen, thereby inducing the presence of the antigen in the circulatory system of the subject. Applicant states that the specification demonstrates that circulating antibodies can migrate across the blood-brain barrier once the blood-brain barrier has been compromised. Applicant indicates that Examples 2(iii), 3-5, and 7 demonstrate that the NMDAR1 protein, when delivered to the circulatory system of a rat model of neurological disease, can be used as an antigen to generate antibodies against the NMDA receptor. Applicant argues that the examples demonstrate that the antibodies against the NMDA receptor can cross the blood-brain barrier, can bind to the NMDA receptor, and can modify the function of the NMDA receptor. Applicant points out that the specification provides

evidence of the neuroprotective efficacy of the claimed method against neurological disorders and in improving cognition in rat models (Examples 3-4 and 7). Applicant also contends that these teachings provide adequate guidance to enable one skilled in the art modify the function of a target receptor associated with a neurological disorder or cognition by raising antibodies against a central nervous system antigen.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Applicant has not provided evidence to demonstrate the modification of the function of any target receptor associated with a neurological disorder in a subject by administration of a peptide vaccine comprising an NMDAR1 antigen. The specification teaches subcloning the full length mouse NMDAR1 cDNA into an adeno-associated virus (AAV) plasmid to yield a recombinant virus, AAVNMDAR1 (pg 54, lines 14-19). The specification also teaches the peroral administration of this vector to groups of rats (pg 54, lines 19-22; pg 59-75). The specification discloses NMDAR1 protein expression and the presence of circulating antibodies in rats administered the genetic vaccine (pg 55-57). However, the specification provides no guidance or working examples for the administration of a NMDAR1 antigen peptide vaccine and modification of the function of any target receptor in a subject. The examples in the specification disclose the delivery of the full length mouse NMDAR1 *gene* into rats while the claims of the instant application recite the delivery of an *antigen* into a subject. The working examples in the specification directed to administration of the genetic vaccine (as reviewed in Applicant's arguments above; see examples 2(iii), 3-5, 7) do not provide guidance regarding the administration of a protein vaccine to subjects. Additionally, the examples in the specification, such as examples 2(iii), 3-5 and 7 teach that antibodies against the NMDA receptor can cross the

blood-brain barrier, can bind to the NMDA receptor, and can modify the function of the NMDA receptor only after the administration of a NMDA1 *genetic* vaccine. However, there is no guidance or working examples in the specification to indicate that if administered, the NMDA *antigen* vaccine produces anti-NMDA antibodies and that the antibodies bind to a target receptor on a neuronal cell to directly modify the receptor or indirectly modify the function of a process involving the receptor *in vivo*.

Furthermore, the specification of the instant application outlines a prophetic procedure for administering a NMDAR antigen vaccine into the circulatory system of the subject. However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily modify the function of a target receptor associated with a neurological disease. Although the claimed method may utilize routine administration techniques, the results of the method are unpredictable and complex when combined with the step of administering an NMDAR1 antigen. As reviewed at pg 8 of the Office Action of 27 February 2002 (Paper No. 16), the state of the art at the time the application was filed indicates that numerous problems exist in regards to administering a subunit (antigen)

vaccine to humans and animals. For example, when some proteins are included in a vaccine, they may be immunosuppressive, but in other cases, the immune responses to proteins may enhance the disease (Babiuk, , LA. *Vaccine 17*: 1587-1595, 1999; pg 1588, col 2). Although antigen vaccines have the advantage of increased safety, their major disadvantages are their low level of immunogenicity and rapid degradation *in vivo*. The rapid degradation *in vivo* may explain the low immunogenicity, even if linked to a carrier or strong adjuvant (pg 1588, col 2; pg 1590, col 2). Therefore, the skilled artisan would not be able to predict that administration of a NMDAR1 antigen into the circulatory system of a subject would elicit the product of antibodies, which upon compromise of the blood-brain barrier, would pass into the CNS and bind to a target receptor located on a neuronal cell in the CNS and associated with a neurological disorder to modify the function of the target receptor.

(ii) Applicant asserts at pg 26 of the Response (11 February 2003) that the claims which recite the term "neuronal cell" have been amended to recite antibodies that "bind to a target receptor <u>located</u> on a neuronal cell in the central nervous system of the subject <u>and associated with a neurological disorder</u>". Applicant contends that these amendments are sufficient to overcome the examiner's concerns that the term "neuronal cell" is too broad to be enabled by the present specification. Applicant argues that these claims do not cover any or all neuronal cells, but rather the claims are directed to neuronal cells that have the desired target receptor and that are associated with a neurological disorder, a neuroendocrine disorder, or cognition.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action, numerous types of neuronal cells are present in the

central nervous system of a subject, such as dopaminergic neurons, serotonergic neurons, motor neurons, sensory neurons, mesencephalic neurons, hippocampal hilar neurons, oligodendrocytes, Schwann cells, and astrocytes, among others. Undue experimentation would be required of the skilled artisan to determine which specific neuronal cells express the appropriate target receptor and are also associated with a neurological disorder. Different types of neuronal cells express different populations of receptors and one skilled in the art cannot assume that all neuronal cells in the central nervous system will express the target receptor recited in the claims.

(iii) Applicant contends that the specification provides adequate teaching and guidance to enable one of ordinary skill in the art to make and use the claimed methods of the invention to modify the function of a variety of target receptors associated with neurological disorders. Applicant also discusses that the working examples provided by the specification are merely illustrative of the underlying inventive concept of the invention and do not represent the sum total of the underlying inventive concept. Applicant also asserts that adequate guidance has been provided for other suitable target receptors that can be substituted and used in the claimed methods. At pg 31 of the Response, Applicant also indicates that a person of ordinary skill in the art would be familiar with a large number of target receptors associated with neurological disorders. Applicant asserts that it would not be undue experimentation to identify other target receptors, such as NMDA receptors, neuronal glutamate receptors, g-aminobutyric acid receptors, nicotinic acetylcholine receptors, serotonin receptors, and dopamine receptors. Applicant argues that once the skilled artisan is aware that neurological diseases can be treated, or cognition improved, by the production of circulating antibodies, it is merely routine

experimentation to run the identified target receptors through the claimed methods in order to test their efficacy in treating neurological disorders. Applicant contends that adequate guidance has been provided for a number of *in vivo* animal models of neurological disorders, which can be used to test the efficacy of any alternative NMDA receptor subunit antigens or alternative suitable target receptors. Applicant asserts that a number of behavioral tests to determine cognitive effects, if any, that accompany the use of other suitable antigens or target receptors, have been disclosed.

Applicant's arguments have been fully considered but are not found to be persuasive. Although one skilled in the art may be familiar with large numbers of receptors associated with neurological disease, undue experimentation would be required of that person to determine which specific target receptor(s) binds the antibodies generated from the administration of NMDAR1 antigen and is functionally modified. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". The specification of the instant application does not disclose the identity of any target receptor other than the NMDA receptor to which anti-NMDAR1 antigen antibodies will bind and modulate the function of. Applicant's broad brush discussion of testing target receptors through the claimed methods constitutes an invitation to experiment by trial and error. This is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to modify the function of any target receptor

associated with a neurological disorder by administration of an NMDAR1 antigen vaccine, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the response and longevity of the antigen vaccine *in vivo* (see discussion and recited reference), and the breadth of the claims which embrace all possible neuronal cells and all possible target receptors, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
April 24, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER